AUTO-IMMUNITY IN MAN AND HOMOLOGOUS DISEASE IN MICE IN RELATION TO THE MALIGNANT LYMPHOMAS

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DURING the past few years there has been a revival of interest in immunological theories of origin of neoplastic disease. Besides the general theory advocated by Green (1954) there has been work on the auto-immune hæmolytic state associated with some tumours (Dacie 1954, 1955, Rappaport and Johnson 1955). Rosenthal et al. (1955) found Coombs-positive tests in patients with lymphatic leukæmia and lymphosarcoma. Green et al. (1957) thought that the anæmia of advanced malignant disease might usually be due to an auto-antibody produced by the tumour mass but when they looked for evidence of this they found it chiefly in patients with tumours of the reticuloendothelial system.

Working from two different sets of observations we recently suggested independently an explanation on these lines, to account for some of the puzzling clinical features presented by the malignant lymphomas. One of us (H. S. K.) was comparing the activity of isologous *versus* homologous mouse bone-marrow on lymphoid tumour production following irradiation. This work led to a series of experiments designed to elucidate the nature of a fatal wasting disease which appeared in F_1 hybrid mice injected with hæmatopoietic cells from parental strain donor animals (Kaplan and Rosston 1959b). It was found that the disease developing in these animals was due to the destruction of their lymphoid cells by the injected donor cells. The anæmia and wasting disease observed under these conditions seemed to be an experimental counterpart of the Coombs-positive hæmolytic anæmia and the "toxic" cachexia sometimes seen in patients with malignant lymphomas.

Clinical observation of patients with Hodgkin's disease led the other (D. W. S.) to look for an explanation of the fever, variation in lymph-node size, some of the skin changes, anæmia, multiple infections, and acute terminal illness seen at times in these cases. These manifestations were not commonly seen with other neoplastic diseases and often occurred with malignant lymphomas before there was any widespread involvement of tissues throughout the body, sometimes resulting in the death of these patients at what appeared to be an early stage of the neoplastic process. Observation of profound lymphatic depletion in a few of these patients together with evidence of failure of immune response led to the suggestion that several of the previously unexplained clinical manifestations of the malignant lymphomas might be due to antigenic differences between the lymphoid tumour cells and the normal lymphoid cells of the patient resulting in normal lymphocytic cell destruction (Smithers 1959). After an exchange of views in San Francisco in January, 1959, we thought that a brief account of the evidence put forward from our two different starting-points resulting in similar conclusions might be of interest if summarised together. We have therefore extracted from the paper presented by H. S. K. and his associates at the meeting of the Western Society for Clinical Research at Carmel in January, 1959, a brief account of their thesis and of the evidence obtained from animal experiments, added an abstract of the clinical observations on this subject presented by D. W. S. in the Robert Knox memorial lecture given at the Royal College of Surgeons in London in May, 1958, and concluded with a few comments on the development of what appears to be the equivalent of "homologous disease" in mice in some patients with malignant lymphomas.

Homologous Disease in Mice

The rising interest in tissue transplantability and chimeras has uncovered a series of experimentally induced diseases in mice which have a number of common features. These have been called "parabiosis intoxication", "secondary disease", "runt disease", and "wasting disease".

The majority of rat pairs placed in parabiosis with a cross-circulation develop "parabiosis intoxication", in which one animal remains well while the other rapidly loses weight and dies with a profound atrophy of lymphoid organs and loss of fat. This disease has been known for some forty years at least and attributed to unfavourable reactions between the blood of the two animals resulting in hæmolysis in one partner (Finerty 1952). When homologous rats are separated after a few days in parabiotic union a previously exchanged skin graft may remain viable in an animal which is dying with general lymphoid atrophy, complete disappearance of the thymus, and immunological paralysis (Nakic and Silobrčic 1958). A few of these animals which recover from this disease then show destruction of the graft.

Spleen and marrow cells injected into lethally irradiated mice may survive and repopulate the hæmatopoietic tissues preventing acute radiation death (Ford et al. 1956). This may be followed by death from delayed or "secondary disease" in which the animals lose weight and die with marked atrophy of lymphoid tissue (Barnes and Loutit 1956). Animals protected against lethal irradiation in this way with homologous cells may accept skin grafts from the homologous donor strain (Main and Prehn 1955), but if they are restored to immunological competence by injections of isologous cells they will then slough off their skin homografts (Trentin 1956, 1957, Main and Prehn 1955). Animals dying of "secondary disease", however, do not slough their homografts, because their autologous immune mechanisms are suppressed. In "secondary disease" the homologous donor cells appear to be reacting immunologically against the host (Feldman and Yaffe 1958).

When very young mice are injected with spleen cells from a homologous donor (Billingham 1958), they also develop a disease with marked loss of lymphocytes and atrophy of the thymus, lymph-nodes, and spleen. This has been called "runt disease". A similar disease has been reported in chicks (Simonsen 1957). These young animals are immunologically immature, while the adult cells injected are immunologically competent. The injected cells react against the new antigens they meet and destroy the lymphoid cells of the recipient.

Several workers came upon the fourth variant in the series, called " wasting disease ", at about the same time but for different reasons (Schwartz et al. 1957, Trentin 1957, Uphoff 1957, Cole and Ellis 1958, Kaplan et al. 1958). Hæmatopoietic cells from parental strain donors injected into F_1 hybrid mice produce a fatal wasting disease with anæmia and gross loss of host lymphatic tissue and fat. The F_1 hybrid mice are able to accept tissue grafts from either parental strain because they have the antigens of both, but neither parental strain will accept F_1 hybrid tissues because they react to the antigens of the other parent in the hybrid cells. Parental strain lymphoid cells may survive and proliferate in F_1 hybrid hosts and make antibody to the foreign host antigens derived from the other parent. The parental lymphoid cells react immunologically on contact with these host antigens. Lymphoid cells from very young parental strain donors are too immature to produce " wasting disease ". Fœtal cells may be used to protect mice against both lethal doses of radiation and against the development of " secondary disease " (Barnes et al. 1958, Uphoff 1958). Very young recipients, on the other hand, are particularly susceptible to " wasting disease " which they may develop without prior irradiation (Cole and Ellis 1958). Kaplan and Rosston (1959b) suggest that donor lymphoid cells probably die in the course of killing host target cells and that the killing process involves direct contact between each donor cell and a very few target cells. The severity of " wasting disease " depends on the number of donor cells injected (Cole and Ellis 1958) and on the dose of prior irradiation given to the host (Kaplan and Rosston 1959b), in other words on the number of host lymphoid cells destroyed. Augmentation of host lymphoid tissue by prior adrenalectomy reduces the animal's susceptibility to " wasting disease " for a given number of injected cells (Kaplan and Rosston 1959a). Small doses of cells produce slight weight loss with recovery, large doses are usually fatal. A few cases of apparent recovery in mice whose cage mates died of " wasting disease " suggest that they may have been made chimeric by complete destruction of hybrid lymphocytes followed by a repopulation with donor lymphocytes left over from the struggle (Kaplan and Rosston 1959b). The chimeric nature of such mice has not yet been tested by another inoculation of parental strain lymphoid cells.

Trentin (1957) proposed the name " homologous disease " to cover all the complications arising from successful transplantation of homologous lymphoid cells to tolerant hosts. It seems probable that " parabiosis intoxication ", " secondary disease ", " runt disease " and " wasting disease " are all closely related variants of " homologous disease ". Wasting, anæmia, and lymphoid cell depletion are the common factors, and all seem to be due to a reaction of foreign lymphoid cells against target cells in the host. They vary in the different reasons why the host fails to destroy the foreign cells introduced. These may be immunological paralysis with " parabiosis intoxication ", radiation injury in " secondary disease ", immaturity in " runt disease ", and hybrid genotype in " wasting disease ".

There is some indication that total ablation of the lymphoid system of an animal (which may occur without total body irradiation) may be incompatible with life. It appears that the anæmia of " homologous disease " may be due to a combination of destruction of erythroid precursors in the host by lymphoid cells from the donor, resulting in a fall in erythrocyte production, and of hæmolysis and/or erythrophagocytosis of the host red blood-cells as well. Simonsen (1957) found Coombs-positive anæmias in his chicks with " homologous disease ". The mechanism of profound weight loss in " homologous disease " is not understood. Preliminary studies suggest that animals with " homologous disease " may have a decrease in serum-protein with a special fall in the gamma-globulin fraction.

Homologous Disease in Man

The recognition of auto-immunity in man where a patient's serum contains antibodies against some constituent of his own tissues has led to a spate of suggestions that certain well-recognised but ill-understood disease processes might be explained on this basis. Hæmolytic anæmia (Dacie 1954), Hashimoto's disease (Roitt et al. 1956), nephritis (Glynn and Holborow 1952), disseminated lupus erythematosus (Friou 1957, Alexander and Duthie 1958), non-tuberculous Addison's disease (Anderson et al. 1957), and myasthenia gravis (Smithers 1959) have all been entered as candidates with very varied degrees of justification. Neoplasms of tissues concerned with antibody formation may provide a rather special case: lymphoid tumour cells may become immunologically differentiated from the cells of the host, perhaps by " antigenic deletion " (Weiler 1959), but retain the capacity to make antibodies. They would thus acquire the ability to react against and destroy the patient's normal lymphoid and other hæmatopoietic cells. The possibility of a two-way interaction cannot be excluded but seems less probable, for the reason that the tumour cells are more likely to become differentiated from normal cells by the loss of antigens, rather than the acquisition of new ones. Since antibody-forming cells detect the presence of foreign antigens, rather than the absence of familiar proteins, the normal lymphoid cells of the host are not likely to respond to autologous tumour cells which have undergone antigen deletion. Thus the most probable immunological reaction may be postulated as being that of lymphoid tumour cells attacking normal cells, rather than the reverse. The situation may therefore closely parallel that seen in the various forms of homologous disease in mice. Clinical evidence in support of such a concept may be found in some, at least, of the following: (1) the multiple infections and poor immune reactions which occur in patients with malignant lymphomas; (2) the hæmolytic anæmia, wasting, and lymphoid destruction seen in these diseases; (3) the finding of auto-immune antibodies in the blood of these patients; (4) the similarities of expression of some of the known immunological diseases and of the malignant lymphomas; (5) the association of other known auto-immune disease with the subsequent development of lymphoid tumours in the organs or tissues involved; (6) the relation of the spleen and thymus to these diseases; and (7) the response of some to the " toxic " manifestations of the lymphoid neoplasms to treatment with steroids.

The frequency with which some lymphoid tumours, particularly Hodgkin's disease, are associated with infection has long been appreciated. Ewing (1940) said that " tuberculosis follows Hodgkin's disease like a shadow ". Patients with Hodgkin's disease are known to be poor producers of antibodies and they may have negative tuberculin reactions (Dubin 1947) even in the face of active tuberculosis (Parker et al. 1932). They also show a diminished response to the cutaneous application of antigens (Schier et al. 1956) and prolonged survival of cutaneous homografts (Green and Corso 1958, Kelly et al. 1958). Unusual infections abound in Hodgkin's disease, of which torulosis (Zimmerman and Rappaport 1954, Gowing 1958) has received more attention than

most. Patients dying from malignant lymphomas may have a great variety of fungal infections though this may possibly be prominent only because of the suppression of other infections with antibiotics.

Patients with malignant lymphomas suffering an acute terminal illness often develop hæmolytic anæmia and wasting and can sometimes be shown to have lymphatic depletion very similar to that seen in " homologous disease " in mice (Smithers 1959). Laboratory animals with " wasting disease ", although suspected (before the nature of the condition was recognised) of having epidemic infection, are rather surprisingly free of bacteria other than their normal flora (Simonsen 1957, Castermans 1958, Kaplan and Rosston 1959b). This may be due to the protected experimental conditions rather than to any preservation of immune response and has been noted in patients depleted of lymphocytes by total body irradiation. A striking example of the lymphoid depletion which can occur in Hodgkin's disease was seen by one of us in a patient in 1957 (Smithers 1959). This is of such interest that we reproduce here an abstract of her notes mostly taken from Dr. N. F. C. Gowing's postmortem report :

A 41-year-old woman with one year's history from first symptom to death. Block dissection of nodes right side neck March, 1957; nodes involved by Hodgkin's disease. Radiotherapy to mediastinum, both sides of neck, and right axilla May and June, 1957, 1600r per field in 36 days. White blood-cell count on completion 9000 cells per c.mm. Hæmoglobin 13.5 g. per 100 ml. Sudden onset acute illness October, 1957, high fever with rapidly falling white blood-cell count and hæmoglobin to 3100 cells per c.mm. and 8.9 g. per 100 ml., unaffected by chemotherapy (CB 1385) 10 mg. on each of two successive days, prednisolone (100—500 mg. a day for 10 days, total 2200 mg.), penicillin, streptomycin, or nystatin except that white blood-cell count continued down to 1000 cells per c.mm. and hæmoglobin to 7.9 g. per 100 ml. in 7 days. Died November, 1957, after only three weeks of illness. Nowhere could any evidence of residual Hodgkin's disease be found, all lymph-nodes showed a remarkable loss of lymphoid tissue, all that remained being a reticulum-cell network. Marked hypoplasia of bone-marrow almost amounting to aplasia was present. Lymphoid tissue in spleen was greatly reduced in amount. Pulmonary aspergillosis and multiple staphylococcal abscesses, localised left staphylococcal empyema, and moniliasis of pharynx and œsophagus were all found.

Auto-immune antibodies have been found in the blood in some patients with lymphomas. André et al. (1954) and Lacassagne and Bessis (1954) described the case of a woman with aleukæmic lymphatic leukæmia who showed auto-antibodies and destruction of her white blood-cells. A splenectomy was performed with subsequent decrease in the titre of anti-leucocytic auto-antibodies. The spleen, microscopically, showed most interesting features similar to those of Hodgkin's disease.

There are some striking similarities between certain known immunological disorders and some manifestations of the lymphomas. Acquired hypogammaglobulinæmia is associated with splenomegaly and hæmolytic anæmia (Prasad et al. 1957), and may be followed by chronic lymphatic leukæmia (Jim and Reinhard 1956), or by tumours of the thymus (Good 1954, Soutter et al. 1957). Abnormalities of liver and spleen occur in Hashimoto's disease, and Luxton and Cooke (1956) thought that the reticuloendothelial system as a whole might be damaged. A palpable spleen associated with thyroid enlargement is suggestive of Hashimoto's disease.

There is not a great deal of evidence to support the suggestion that there is a higher incidence of lymphoid tumours in organs which have been the site of auto-immune reaction than in those which have not (Smithers 1959) but there have been several reports of the appearance of lymphoid tumours in the thyroid following Hashimoto's disease (Graham and McCullach 1931. Lindsay and Dailey 1955, Walt et al. 1957). Reticulosarcoma of the thyroid or " struma reticulosa " was commented on by Brewer and Orr in 1953 in the following interesting manner :

" It is not impossible that the ' struma reticulosa' with which we are now dealing might be a variant of Hashimoto's struma where, as a result of greater activity, the predominantly lymphoid cells have been replaced by larger mononuclear cells, possibly as the result of some type of hypersensitive reaction."

Splenectomy may have a profound effect on neutropenia, pancytopenia, and Felty's syndrome (Edwards 1951, 1955, Orebaugh and Coller 1955) ; aplastic anæmia may be cured by thymectomy (Humphreys and Southworth 1945, Soutter et al. 1957) or helped by splenectomy and corticotrophin (Heaton et al. 1957). The lymphoid hyperplasia of the thymic medulla in myasthenia gravis is said by Castleman (1955) to be similar to that seen in the thyroid in Hashimoto's disease. Agammaglobulinæmia may be associated with a thymoma (Good 1954, Martin et. al. 1956, Ramos 1956) and with chronic lymphatic leukæmia (Jim and Reinhard 1956).

The response of some patients with malignant lymphomas to steroid therapy is dramatic if temporary. Long-standing fever may subside immediately, hæmolytic anæmia may be checked, and the exfoliative dermatitis which can occur with these diseases may be arrested (Fergusson et al. 1958). These effects have been attributed to the powerful inhibitory effect of the adrenal oxysteroids on immunological reactivity in general.

The implications of this theory, if proved correct, in the treatment of patients with lymphoid neoplasms are clearly of great importance. While irradiation of sensitive tumour masses in a patient with malignant lymphoma may be most beneficial, large-field irradiation of uninvolved regions in the early stages may possibly have a detrimental effect by precipitating " homologous disease " through normal lymphoid cell destruction. Similar considerations would apply to the use of the nitrogen mustards in large doses at this stage. The benefits obtained with systemic treatments such as chemotherapy or radioactive phosphorus have sometimes been most obvious when the " toxic " manifestations have been greatest and the neoplastic manifestations insignificant. Wide-field abdominal irradiation has been practised with temporary benefit for many patients with Hodgkin's disease who have developed fever but have little or no obvious residual lymph-node enlargement. These more general treatments may be affecting the balance between the warring lymphoid cells of the tumour and the host which remain in the circulation after the main tumour masses have responded to local irradiation. A reappraisal may be needed of the time to use chemotherapy and total-body or even large-field irradiation, in relation to the degree and localisation of tumour formation and the destruction of the host lymphocytes and hæmopoietic tissues going on in each patient with a malignant lymphoma.

Summary

" Homologous disease " in animals and lymphoid neoplasia in man have many similar features. It would seem that the wasting, anæmia, and lymphoid depletion observed in both groups of diseases may well be due to a cyto-immunological reaction of lymphoid cells (tumour or homologous) against the usual hæmatopoietic cells of the host. This theory would explain many of the puzzling clinical features chiefly associated with Hodgkin's disease but also with lymphatic leukæmia and lymphosarcoma at times, and rarely even with reticulum-cell sarcoma and

multiple myelomatosis. Some of the evidence which led us to reach the same general conclusion from two quite different approaches has been briefly presented here. While speculations about possible therapeutic applications are of great interest, the present need would seem to be for both more animal and clinical research designed to clarify our ideas about the previously unexplained clinical manifestations of the malignant lymphomas. The recognition of "homologous disease" in mice and autoimmune disease in man may have opened the way.

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HYPERVENTILATION FOR THE MAINTENANCE OF ANÆSTHESIA

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Crile (1921) believed that loss of consciousness alone was not sufficient to protect the patient during surgery from the reflex effects of painful stimuli. This view has recently received support from Loder (1957), who was not satisfied with the general condition of patients submitted to surgery under the light narcosis commonly used with relaxants: he noted pallor and sweating, and found that severe stimuli, such as traction on the mesentery, gave rise to a typical vasovagal response. He also observed that postoperatively the patients were not as alert and responsive as one would expect after light narcosis. Infiltration of the cœliac plexus with a local anæsthetic diminished these effects. If Loder's interpretation is correct, those of us who have been using ever lighter narcosis over the past years should have seen this picture frequently. During combined nitrous-oxide (N_2O) and relaxant anæsthesia we frequently do not use thiopentone, and rely on nitrous oxide alone for induction and narcosis. Analgesics such as pethidine or alphaprodeine are of little value in modifying the autonomic reflexes during abdominal operations; and it is well known that these reflexes are not completely abolished even by deep ether anæsthesia.

There are two possible reasons why we do not see a vasovagal response more often. The first is our insistence on full doses of relaxants and absolute muscle flaccidity; for the surest way of avoiding vasovagal collapse is gentle surgery associated with adequate relaxation. The second may be effective control of respiration, an important component of the light narcosis with relaxant technique (Gray and Rees 1952).

Dundee (1952) showed that controlled respiration increased the duration of the narcosis produced by anæsthetic drugs; also, when respiration was controlled, the dose of thiopentone required to maintain anæsthesia was significantly less than when respiration was assisted but spontaneous. After two hours the dose of relaxant also tended to be less.

In those patients for whom thiopentone is omitted, we have been using N_2O to induce anæsthesia; and for maintenance the concentration is never less than 70% with O_2. This is a concentration known to give narcosis but not sufficient to prevent brisk movement in response to painful stimuli. The dose of relaxant modifies to some extent this response. Shea and his colleagues (1954) have estimated that in a healthy man 200—400 mg. tubocurarine may be needed to prevent all muscular activity; it is therefore not surprising that occasional movements are seen with the customary dose of 40—50 mg. With our technique therefore the N_2O and relaxant drug do not by themselves prevent movement; but when they are used in combination with controlled respiration the patient is completely unresponsive. This cannot be accounted for by a synergistic action of these two drugs, for N_2O has no effect on muscles and in all probability relaxants in clinical dosage do not depress the central nervous system.

Dundee (1952) investigated the pH of blood under anæsthesia administered by different anæsthetists; and he found that patients who had respiration

controlled were almost always in a state of respiratory alkalosis, while those in whom the respiration was assisted tended to be acidotic. In conscious subjects hyperventilation to the point of respiratory alkalosis causes dizziness and confusion, often associated with characteristic delta waves on the electroencephalogram; extreme overbreathing can result in loss of consciousness. Clutton-Brock (1957) suggested that it may also raise the pain threshold. Variations in CO_2 tension produce even greater changes in cerebral blood-flow and electroencephalogram patterns than do variations in oxygen tension.

During N_2O-relaxant anæsthesia, with monitoring of the electroencephalogram, waves of the delta type (2—3 per second) have been demonstrated when the patient is hyperventilated. This paper reports our findings and an attempt has been made to correlate alterations in blood pH with this appearance of slow-wave activity.

Experimental Procedure

Anæsthesia.—Adult patients were premedicated with promethazine ('Phenergan') 25 mg. and atropine 0.65 mg. After pre-oxygenation for five minutes to eliminate nitrogen, a test-dose of 5 mg. tubocurarine was given and anæsthesia was induced with N_2O. After a further 25—30 mg. tubocurarine the patient was intubated and maintained on N_2O (70%) and O_2 supplemented with additional doses of relaxant to ensure complete flaccidity and to permit control of respiration (Gray and Riding 1957).

Electroencephalographic monitoring.—An 'Ediswan' two-channel portable electroencephalograph was coupled to the patient before induction, and a fronto-occipital unipolar lead was used for intermittent monitoring during anæsthesia.

Estimation of blood pH.—After the application of warm packs, "arterialised" venous blood was obtained by puncture close to the wrist, and the pH was estimated in an anaerobic three-arm assembly in a thermostatically controlled water-bath. This method of sampling, while not giving absolute values, has been shown to give a reliable indication of alterations in pH (Brook et al. 1957).

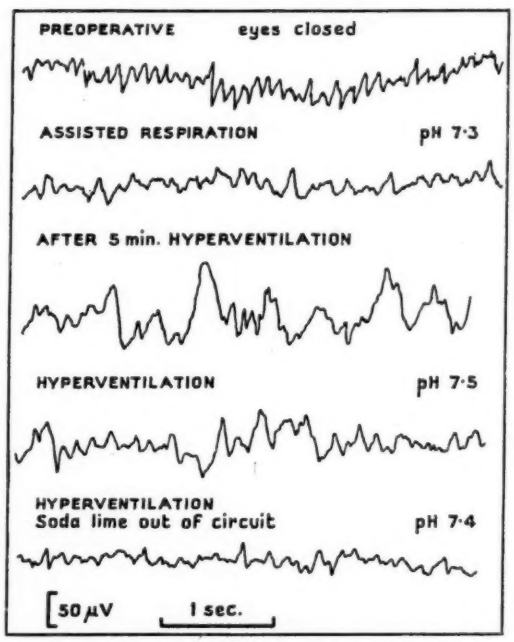
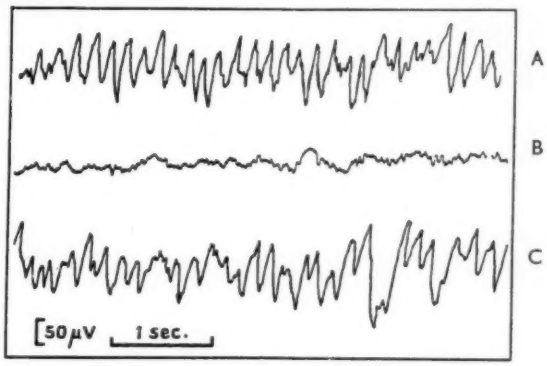


Fig. 1—Electroencephalogram (fronto-occipital lead) of a woman aged 43 during mastectomy under N_2O-relaxant anæsthesia.

It shows slow-wave activity following hyperventilation associated with a rise in pH. In the final tracing the soda-lime cannister was bypassed; and there is a disappearance of the large-amplitude slow waves associated with fall in pH.



A	B	C
Hyperventilation	Hyperventilation	Hyperventilation
N_2O 2 litres	N_2O 2 litres	N_2O 2 litres
O_2 1 litre	O_2 1 litre	O_2 1 litre
CO_2 none	CO_2 400ml. 3 mins.	CO_2 none 7 mins.
Absorber in	Absorber out	Absorber in

Fig. 2—Electroencephalogram (fronto-occipital lead) of a woman aged 62 during cholecystectomy under N_2O relaxant anæsthesia.

After the introduction of CO_2 the large-amplitude slow waves disappear; but they return when the CO_2 is eliminated.

Results and Discussion

Fig. 1 shows the appearance of slow-wave activity and associated pH changes during N_2O-relaxant anæsthesia in a patient undergoing mastectomy.

It has been suggested by Davis and Wallace (1942) that these changes in the electroencephalogram are produced by vasoconstriction which reduces the supply of both O_2 and glucose to the cerebral cells. This anoxic theory has been suspect since Kety and Schmidt (1946) showed that, though at a pH of about 7.5 cerebral blood-flow is reduced by a third, the O_2 uptake by the brain is not in fact diminished. It has also been shown by Holmberg (1953) that with pure hypoxia (down to 62% arterial O_2 saturation), but with a normal alveolar CO_2 tension, produced by the inhalation of a mixture containing 6.5 parts O_2, 4.5 parts CO_2, and 89 parts nitrogen, there is no change in the electroencephalograph and no slow-wave activity.

Morrice wrote in 1956 that lack of CO_2 is the important factor in producing slow waves in the electroencephalogram. Bonvallet and Dell (1956) have shown that an excess of CO_2, has an excitatory effect on the ascending activating reticular formation, and that during the hypocapnia which follows hyperventilation, activity in the reticular formation is diminished or absent. These authors have suggested, moreover, that an adequate CO_2 tension is as essential for the proper functioning of the mesencephalic reticular substance as it is for the bulbar respiratory centre. Morrice (1956) has also put forward the hypothesis—for which admittedly there is as yet little direct evidence—that CO_2 is essential for the Krebs tricarboxylic-acid cycle: lowering the CO_2 tension in blood "alters the rate and direction of the cycle". If such a hypothesis proved correct it would bring hyperventilation, as we use it in anæsthesia, into line with one suggested action of anæsthetic agents.

Fig. 2 shows the disappearance and return of the slow-wave pattern as CO_2 is first introduced and then washed out. During the administration of CO_2 this patient began to move and required a further dose of *d*-tubocurarine. The effect of hypocapnia is then probably mediated by the reticular formation which, by its radiation to the cortex, maintains our wakefulness. The reticular formation is affected also by analgesics and

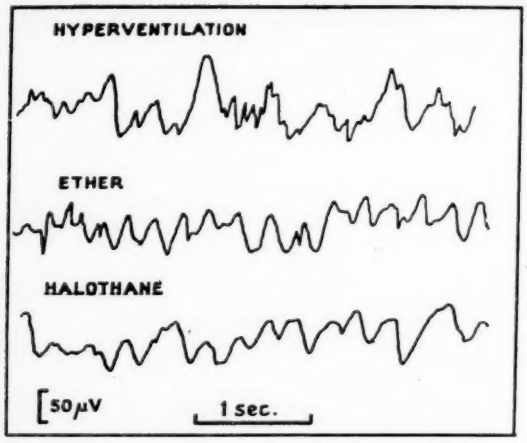


Fig. 3—Similar slow waves produced by hyperventilation, ether, and halothane.

anæsthetic agents, and the electroencephalographic patterns of hyperventilation and of certain planes of ether and halothane anæsthesia are similar (fig. 3).

Avery et al. (1956) have used hyperventilation to produce sedation in severe crush injuries of the chest, while Shea et al. (1954) reported a case where, after induction with a small dose of thiopentone, the patient was maintained on tubocurarine only and O_2 for no less than seven and a half hours. Electroencephalography showed that the effects of the thiopentone lasted for only about an hour. These authors postulated a central effect of tubocurarine, but hyperventilation seems to be a possible explanation.

Conclusion and Summary

The substitution of hyperventilation for potent anæsthetic drugs has many advantages. It is, above all, controllable; and, since CO_2 is a normal metabolite, recovery from it is rapid.

Those anæsthetists who insist on retaining spontaneous respiration point to the circulatory disturbances of controlled respiration; but ventilation, even by hand, need not be accompanied by serious circulatory effects, and the objection is completely invalid if a "Pulmoflator" with a negative pressure phase is employed. Many anæsthetists are horrified if they see a full dose of relaxant and controlled respiration being used for such minor surgical procedures as hæmorrhoidectomy or herniorrhaphy; they commonly describe this as taking a "sledgehammer to crack a nut". To the patient, however, the anæsthetic risks are the same, whatever the operation; and we believe that this "sledgehammer" technique allows good control and that it is less toxic than anæsthesia with more potent agents, such as ether or halothane, used with spontaneous respiration.

In summary, we use hyperventilation as a supplementary anæsthetic agent; and our experience over many years has convinced us that it is both harmless and conducive to good operating conditions.

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Preliminary Communication

INHIBITION OF CHOLESTEROL ATHEROSCLEROSIS BY IMMUNISATION WITH BETA-LIPOPROTEIN

It is generally agreed that the characteristic serum-lipid alteration in atherosclerosis is an increase (both relative and absolute) in the level of the low-density β-lipoprotein fraction. According tho the "filtration" theory of atherogenesis, deposition of cholesterol in the arterial wall is enhanced by plasma-lipoprotein alterations and by changes in the subendothelial ground substance.

In rabbits Baker and his coworkers[1] succeeded in preparing antisera against serum-lipoproteins obtained from hypercholesteræmic dogs kept on an atherogenic diet. Following these observations, we have tried to influence the course of atherosclerosis, induced by cholesterol feeding, by immunisation with β-lipoprotein.

Method

For 12 weeks Leghorn cocks and rabbits were given a cholesterol supplement to their diet—2 g. daily for the fowls and 1 g. for the rabbits. From the plasma of these animals the β-lipoproteins were isolated by ultracentrifugation (at 145,000 G.) using a modification of the technique of Gofman et al.,[2] and these lipoproteins were used as antigens for crossimmunisation.

1. Baker, S. P., Ogden, E., Riddle, J. W. *Tex. Rep. Biol. Med.* 1951, **9**. 391.
2. Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H., Strisower, B. *Circulation*, 1950, **2**. 161.

Ten rabbits and ten cocks were given, once a week, an intramuscular injection of alum-precipitated antigen containing 22·5 mg. protein. The rate of antibody formation was measured by an interfacial precipitation test; and after 6 weeks, every serum was found to show titres in excess of 1/10,000. Examination of these sera with immunoelectrophoresis revealed the presence of anti-β-lipoprotein.

When this immunisation schedule was finished, the immunised group of rabbits and an equal number of non-immunised rabbits were fed for 16 weeks with 1 g. cholesterol daily. The immunised group of cocks and an equal number of non-immunised cocks were given 2 g cholesterol daily. During this time, the immunised group received two more antigen injections.

Results

The changes in the average cholesterol level of the plasma were:

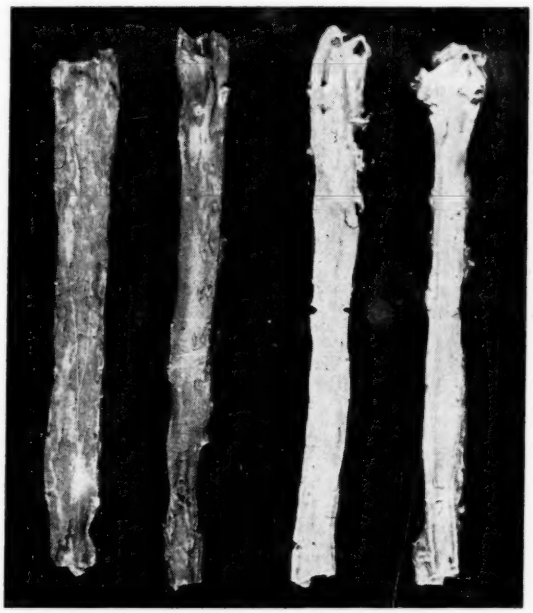
CHANGES IN PLASMA-CHOLESTEROL (mg. per 100 ml.)

—	Rabbits		Cocks	
	Immunised	Non-immunised	mmunised	Non-immunised
Before immunisation ..	65	65	185	183
After immunisation ..	153	..	230	..
After cholesterol feeding	600	710	332	560

The immunisation itself was followed by a rise in plasma-cholesterol. The level after cholesterol feeding revealed species differences. Thus in the two groups of rabbits it was nearly identical, but in the immunised

cocks it was markedly lower than in the non-immunised ones, though still high enough to produce atherosclerosis.

After 16 weeks all the animals were killed and the blood-vessels were examined. The aorta of the non-immunised groups had developed atherosclerosis characteristic of cholesterol feeding, but the vessels of the immunised groups showed only insignificant changes.



(a) (b)

Aortas of cholesterol-fed rabbits, stained with Sudan III. (a) Non-immunised rabbits. (b) Immunised rabbits.

The difference was even more striking after treatment of the vessels with Sudan III which produces a bright red colour in the lipoid-infiltrated parts. Whereas the vessels of the immunised group exhibited only small sudanophil spots, those of the non-immunised group were diffusely stained (see fig.).

Hence immunisation with β-lipoprotein inhibited the development of experimental atherosclerosis in both species. In forthcoming experiments we hope to determine the specifity and the mode of action of this effect.

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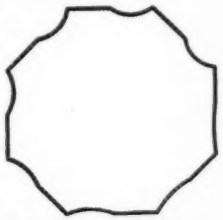
"... And you *become* rather than learn to be a doctor ... You can learn to be a technician, and some qualified doctors never get beyond being good, although often exceedingly good, technicians. But you can only *become* a 'doctor' in the real sense, be it general practitioner, consultant, specialist, physician, surgeon or gynæcologist." — A. E. CLARK-KENNEDY. *How to Learn Medicine*; p.12. London, 1959.

New Inventions

INSTRUMENT FOR ESTIMATION OF CLUBBING

CLUBBING of fingers and toes is found most often in cyanotic congenital heart-disease, bronchial carcinoma, and bronchiectasies. Clubbing is usually registered as a clinical impression only; and this may explain some of the differences in reported incidence, and possibly some of the differences in reported effect of vagotomy or hilar denervation. A quantitative expression of the clubbing would be useful, and some methods have been described for this purpose. Cudkowicz and Wraith[1] estimated the degree of clubbing by measuring the water displacement of the distal two centimeters of the right thumb.

With clubbing of fingers and toes the nails usually have an increased longitudinal curvature. We have lately tried to estimate the degree of clubbing by measuring this longitudinal curvature of the nails. For this purpose we have used an instrument made from a thin, octagonal sheet of brass, with a different curve filed into each of the eight sides (see figure).



Instrument for measuring longitudinal curvature of nails.

Each curve is the arc of a different circle, the radius of which varies from 6·4 mm. for the sharpest curve to 42 mm. for the slightest curve (see table I).

The different circles were first drawn on thin cardboard with a compass, and then accurately cut out with a pair of scissors. A goldsmith (Mr. T. Ysted, of Porsgrunn) filed a curve to fit each circle into the leftmost 10 mm. of each of the eight sides of the octagonal sheet of brass.

The maximal distance between a 10 mm. long chord and its arc will be different for each of the eight circles, and will represent the depth of the deepest point of the respective curve. The maximal distance from a 10 mm. long chord to its arc is 0·3 mm. for the slightest curve, and increases by 0·3 mm. for each curve up to 2·4 mm. for the sharpest curve. Table I lists the circle radius and corresponding chord-arc distances for each of the eight curves.

TABLE I—MAXIMAL DISTANCE FROM A 10 MM.-LONG CHORD TO ITS ARC, AND THE CORRESPONDING CIRCLE RADIUS

Curve no.	Chord-arc distance (mm.)	Circle radius (mm.)
1	0·3	42
2	0·6	21
3	0·9	14
4	1·2	11
5	1·5	9
6	1·8	7·8
7	2·1	7·0
8	2·4	6·4

When we use the instrument, we register the curve which exactly matches the longitudinal curvature of the nail. If no curve matches exactly, we register the instrument curve which is slightly more curved than the nail. All the patient's fingernails are measured; the chord-arc distances are added together, and the total is divided by the number of nails measured, in order to obtain the average chord-arc distance for the patient's nails. We measure the longitudinal curvature along the midline of the nail, and measure the 10 mm. with the greatest curvature if the curvature is not the same all the way.

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In order to evaluate the accuracy of the method, the fingernails of eight persons were measured three times, and the previous figures were not made available during the second and third examinations. Table II lists each person's average chord-arc distance for each of the three examinations. In three cases the average chord-arc distance is the same all three times; in three cases it varies within 0·03 mm., in one case within 0·06 mm., and in one within 0·07 mm. Case 1

TABLE II—AVERAGE CHORD-ARC DISTANCES (MM.) FOR EXAMINATIONS I, II, AND III

Subject no.	Examination no.		
	I	II	III
1	0·93	0·96	0·96
2	0·87	0·84	0·84
3	0·84	0·84	0·84
4	0·66	0·66	0·60
5	0·60	0·60	0·60
6	0·51	0·54	0·54
7	0·47	0·40	0·43
8	0·30	0·30	0·30

gave a clinical impression of slight clubbing, cases 2 and 3 a suggestion of clubbing, and cases 4-8 no sign of clubbing.

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Reviews of Books

Science, Medicine and Morals

CHARLES E. RAVEN, D.D., D.SC., F.P.A. London: Hodder & Stoughton. 1959. Pp. 182. 15*s*.

WE are privileged, Dr. Raven feels, to be living in the greatest critical period that humanity has ever known; and the cause of the crisis, as he sees it, is that for 300 years mankind has been increasingly confronted with a conflict between traditional religious views and the new outlook which has developed from scientific thought. This development he traces historically, rather on the lines followed in his Gifford lectures. But when he turns to the "new look", first upon man and his nature and then upon the Universe, he somewhat disappoints the expectations aroused by his previous writings. He dismisses in a few lines "the sort of interpretation which seems to satisfy Sir Julian Huxley" on the ground that "it really does not stand up to criticism". But his criticism of it falls short of the detailed reasoned and constructive comment which evolutionary humanism needs at this stage, both for its own sake and for the sake of its antagonists. Discussing, towards the end of his book, the problem of pain and the problem of evil, he makes an interesting distinction between personal and communal responsibility for evil—on the ground that "the major evils that confront us are evils for which no one individual, however important in his own and other people's eyes, is responsible." It would have been instructive to hear this thesis discussed from the standpoint of evolutionary humanism on one side and traditional religion on the other.

Although the book is based on lectures given at a medical school, the relation of medicine to the problems considered does not clearly emerge. What does seem to emerge is that the gulf between science and religion remains unbridged. And we cannot accept the comfortable answer that there is no conflict between them when, to an increasing extent, they offer different accounts of the world and consequently give different guidance on practical affairs.

The Hand: Its Anatomy and Diseases

JOHN J. BYRNE, M.D. professor of surgery, Boston University School of Medicine. Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 384. 80*s*.

Human hands are often the agents by which the body investigates, and endeavours to manipulate and control, its immediate physical environment; so it is not surprising that they are subject to a wider variety of traumatic insult than any other part of the body, and some of the fascination of hand surgery lies in this variety. How different the forms hand wounds may take is well brought home by that section of Professor Byrne's new book devoted to "special injuries". The important characteristics of some of these (such as indelible-pencil wounds) are well known: and with others, such as radiation burns, many doctors will have at least a theoretical familiarity. But how many could describe the results of the injection of molten plastic following the malfunction of high-pressure moulds, or realise that some aerosol bombs, used as insect sprays, &., carry their own peculiar hazards? (If the needle valve blows out, the escape of gas causes intense cooling of the container, which may inflict injuries equivalent to a third-degree burn).

Descriptions of such lesions take up only a small part of the book, but they serve to indicate its comprehensiveness. Three of its five sections cover the anatomy of the hand and the results of different infections and acute injuries. The remaining sections cover the involvement of the hand in systemic diseases, and describe the principles of reconstructive surgery. The only serious criticism of this praiseworthy book is that the brevity with which some topics are discussed rather decreases its value to junior practitioners. But each chapter has an excellent bibliography: and it is good to note that these bibliographies reflect, by the large number of British titles they contain, the increasing contribution that this country is making to the youngest surgial specialty.

Thrills and Regressions

MICHAEL BALINT, M.D., PH.D., M.SC. London: Hogarth Press and Institute of Psychoanalysis. 1959. Pp. 148. 18*s*.

Dr. Balint explains in his introduction that psychoanalysts have latterly taken more interest in objects and object-relationships than in instincts, which were so central in Freud's theoretical system, and that in his own view the development of instinctual aims is fundamentally different from the development of object-relationship. The latter includes, he says, two primitive and unrealistic attitudes, which he designates by the newly coined words "philobatism" (enjoyment of thrills) and "ocnophilia" (dislike of thrills, such as swings and switchbacks provide). The book is largely about these two types of attitude towards danger and security. Dr. Balint enlarges on the theoretical implications of his concept, and emphasises its value in understanding various features of the psychoanalytical situation. His wife contributes a chapter on "distance in space and time", in which she explains that the philobat "transfers part of his libido from direct satisfaction to a skiful overcoming of the unsatisfactory spaces and times between satisfactions", whereas the ocnophil avoids them and tries to deny their existence. Dr. Balint presents his views engagingly but these essays would have more weight if the speculations put forward were backed with more evidence than he supplies.

A Short Practice of Surgery (11th ed. London: H. K. Lewis. 1959. Pp. 1389. 84*s*.).—This work must have influenced almost every doctor qualifying in this country in the past 20 years, and many more besides in other countries: a remarkable achievement of which Mr. Hamilton Bailey and Mr. McNeill Love can be proud. There are two distinct groups of surgical textbooks—those which provide facts and try to enable the student to assimilate them, and those which set out to stimulate reasoned thought. In this country none of our surgical textbooks have yet broken with the didactic tradition; and *A Short Practice of Surgery* is an exception only in so far as it has tried to make itself palatable—to which it owes its great success. It will continue to be in great demand, for it reveals to the student what is in their master's and their examiner's minds and therefore what is expected of them.

The Nature of Stress Disorders (London: Hutchinson Medical Publications. 1959. Pp. 298. 25*s*.)—This book contains the papers read at the 1958 conference of the Society of Psychosomatic Research, and the verbatim record of the discussions. It is well produced, with 16 photographic plates and several figures and tables. Its six parts deal with the relation of stress to three groups of disorders (essential hypertension, pruritic skin conditions, and dyspepsia); experimental stress; stress and occupation; the person in his family setting; the influence of genetic endowment; and the summing-up.

THE LANCET
LONDON 4 JULY 1959

Combined Treatment for Diabetes

THE several oral hypoglycæmic agents have differing modes of action. The sulphonylureas probably exert their main effect by stimulating the secretion of endogenous insulin; for they are ineffective in pancreatectomised animals[1] and man,[2] and in diabetics are effective only when the plasma before treatment contains some insulin activity.[3] In addition, the sulphonylureas decrease the glucose output from the liver even in the presence of hypoglycæmia, whereas insulin does not.[4] Phenethylbiguanide (DB1) and its near relations, on the other hand, lower the blood-sugar mainly by increasing the uptake of glucose in the periphery, and stimulate anaerobic glycolysis with a consequent rise in the level of serum lactate.[5] They decrease the hepatic glycogen level (instead of increasing it, as do the sulphonylureas) and in diabetics cause a gradual increase in arteriovenous blood-glucose difference. Unlike the sulphonylureas the biguanides have relatively little hypoglycæmic action in non-diabetics; and they effectively lower the blood-sugar in the absence of the pancreas, although without preventing ketosis.[6] Unlike insulin, DB1 decreases muscle-glycogen and the conversion of glucose to carbon dioxide and fatty acids in adipose tissue,[7] and decreases pyruvate tolerance.[8] Basically, the biguanides seem to inhibit the coupling of phosphorylation to electron transport, which is a respiratory function at the mitochondrial level.[9] Part, at least, of the hypoglycæmic action of both DB1 and salicylates imitates the Pasteur effect—that is, the stimulus to anaerobic glycolysis, which, like anoxia itself, increases the permeability of the cell membrane to glucose. Insulin is, in fact, the only known hypoglycæmic agent capable of increasing glucose uptake without apparently modifying the aerobic system concerned with maintaining impermeability to glucose.[10]

There have been differing reports of effects of the combined use of insulin and the sulphonylureas, some workers having found no reduction in insulin requirement[11 12] and others a dramatic decrease,[13 14] especially in cases of insulin resistance. MOHNIKE et al.[15] studied the effects of combined treatment with insulin and tolbutamide (a sulphonylurea) in 38 patients and noted a reduction in insulin requirement in 20—mainly cases with onset at a late age and with only a small exogenous insulin requirement. These workers assumed that the lack of response in the remainder was due to the severe lack of functional β cells. VOLK and LAZARUS[16] reasoned that, although the administered insulin would tend to diminish endogenous insulin production, the simultaneous presence of tolbutamide should stimulate it and thus reduce the exogenous insulin requirement of diabetics with viable β cells. This they found to be the case, and it suggested to them the possibility that certain forms of diabetes may be due to a defect in the normal mechanism for stimulating the β cell to increased insulin output. In support of this they cite the fact that the pancreases of many diabetics have good β-cell granulation[17] and considerable amounts of insulin can be extracted from such pancreases.[18] The satisfactory effect of the sulphonylureas in reducing the insulin requirement in the presence of insulin resistance[13] may be associated with the increased output of endogenous insulin, which, unlike the administered insulin, is not neutralised by insulin antibodies. Combined administration of insulin and sulphonylurea is mainly indicated, however, in the treatment of the labile diabetic with onset in maturity whose blood-sugar is irregularly controlled by a steady diet and insulin in adequate dosage. On the combined treatment such diabetics may have less variation in the level of blood-sugar within each day and from day to day, and are less apt to experience hypoglycæmic symptoms especially when reduction in the dose of insulin has proved possible. Such lessened variability of the blood-sugar can be found even when it is not clinically apparent,[19] but in such cases it is probably not justifiable to complicate the standard insulin treatment by adding the sulphonylurea. DB1 can be used in the same way to decrease the lability of unstable diabetics on insulin treatment,[3] which it will do even in the probable absence of endogenous insulin—usually with a pronounced diminution in insulin requirement. The main limitation of this form of combined treatment is the relatively high incidence of gastrointestinal side-effects when the biguanides are given in doses large enough to reduce the blood-sugar satisfactorily.

The difference in the mode of action of the sulphonylureas and biguanides suggests that their hy-

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poglycæmic action would be additive; and, owing to the side-effects of biguanides in fully effective doses, it would clearly be advantageous to administer these drugs in a dosage below that associated with intolerance, relying on the supplementary effect of a sulphonylurea to lower the blood-sugar adequately. Such a combination has been tried by BEASER [20] on a series of diabetics who were inadequately controlled by diet alone or by diet and carbutamide or tolbutamide. The alternative to this combined oral treatment was insulin, which they had all been having. After it had been established that a certain regimen of diet and insulin could stabilise the blood-sugar between defined limits, either a sulphonylurea or DB1 was introduced and the dose of insulin reduced so that the original level of control achieved on insulin alone was re-established. In this way the effectiveness of the oral hypoglycæmic agents could be expressed in terms of their insulin equivalence. BEASER reports in detail the results in four diabetics. In three of them there was an additive effect, and in two the previous requirement of insulin (52 and 17 units) was entirely replaced. No toxic effects of the combined therapy were noted over periods of up to ten months, although there had been dyspeptic side-effects in three of the four when larger doses of DB1 had been used (with less effect) without the sulphonylurea. Such results suggest that a higher proportion of insulin-treated diabetics could be treated effectively by oral agents alone. But, reasonable as this method may seem, its value must be assessed against the success of treatment by insulin. Only long-term studies can establish the place of combined oral treatment.

Detecting Lung Cancer

In the treatment of lung cancer, as of other varieties of cancer, it is claimed that earlier diagnosis would improve results. But the nature of the abnormality cannot be determined until the presence of an abnormality of some sort has been detected; and it is here that the main difficulty lies. Patients in whom the cancer is detected because it is causing symptoms are well known to have a poor chance of surviving: only about a quarter have the tumour removed, and only about 1 in 20 survive for five years. Attempts are being made to diagnose lung cancer more often before symptoms arise; and the fate of patients diagnosed by mass-radiography units gives some indication of the results. By no means all such patients are symptomless. The units may be employed on "surveys", offering a chest X-ray to all who wish to have one; or they may provide a rapid service to general practitioners, enabling them to obtain a prompt X-ray report on their patients with symptoms, BOUCOT et al.[1] report that 250 cases of lung cancer detected in "surveys" included only 43 (17 %) without symptoms, and in another series POSNER et. al.[2] found that only 15% were free of symptoms. Of the 43 patients without symptoms reported by BOUCOT et al., 25 % lived for three years after the abnormality was detected, compared with only 9 % of those with clinically manifest disease. Thus the chances of surviving are better in cases detected before the onset of symptoms; but the chances of finding cancer at this stage are slender. POSNER et al. studied 238 cases found by mass radiography in the Birmingham region in 1956. In "surveys" the rate of detection in men aged 45 or over was 12 per 10,000 examined. BRETT,[3] in North-West London, recorded 2·7 per 10,000 men of all ages. In the U.S.A. BOUCOT and SOKOLOFF [4] obtained 6·9 per 10,000 and with intensive X-ray campaigns bringing in three-quarters of the whole population similar high rates were recorded in Glasgow (8·6 per 10,000 [5]) and in Edinburgh (6·4 per 10,000 [6]).

Detection of symptomless cases at a rate of about 2 per 10,0000 examined may seem hardly to justify the organisation and expense involved. But, although 85 % of those found in "surveys" were recorded as having symptoms (and indeed may have gone to the mass-radiography unit because of them), their cancers had not so far been detected. Presumably the great majority had "smoker's cough" or minor symptoms insufficiently obtrusive to cause them to go to their doctor for advice. In considering the value of mass-radiography units in this country in detecting cancer, two questions may be asked: (1) Does a unit used for "survey" work ("unselective radiography") [3] discover more cases than one doing "G.P.-referral" work ("selective radiography")[3]?; and (2) Does the after-history of patients discovered by unselective radiography differ from that of the patients discovered by selective radiography?

BRETT found 2·7 lung cancers per 10,000 men by unselective radiography and 26.7 per 10,000 by selective radiography. In the series of POSNER et al. the rates were 3 and 87 per 10,000; and in men over 45 years 12 and 195 per 10,000. In Great Britain a mass-radiography unit doing selective radiography will apparently discover about ten times as many lung cancers as one doing unselective or "survey" radiography. BOUCOT and her colleagues in Philadelphia found a five-year survival-rate of 17 % among 100 "survey" patients, 30 of whom had had the tumour resected. This is about three times the rate reported from several other sources in "non-survey" patients. BRETT recorded 55 % resections after detection by unselective radiography and 32 % after detection by selective radiography, with estimated five-year survival rates of (by chance) the same figures—55 % and 32 % respectively. In the series of POSNER et al. only two-year survival-rates were available. Among the "survey" cases the rate was 25 % and among the "G.P.-referral" cases 20 %, with

1. Boucot, K. R., Horie, V., Sokoloff, M. J. *New Engl. J. Med.* 1959, **260**, 742.
2. Posner, E., McDowell, L. A., Cross, K. W. *Brit. med. J.* May 9. 1959, p. 1213.
3. Brett, G. Z. *Tubercle, Lond.* 1959. **40**, 192.
4. Boucot, K. R., Sokoloff, M. J. *Dis. Chest*, 1955, **27**, 369.
5. Glasgow X-ray Campaign against Tuberculosis, 1956. Official report, compiled by Sir Kenneth Cowan and others. Glasgow: Corporation of the city.
6. Seller, H. E., Welstead, A. G., Williamson, J. *Tubercle, Lond.* 1958, **39**, 339.

resection rates of 44 % and 30 % respectively. Two years after operation 44 % of the "G.P.-referral" patients were alive, but only 38% of the "survey" patients. With such small numbers of patients this difference may be due to chance. There is in this series (unlike that of Boucot et al.) no indication that the patients detected by unselective radiography fared much better than the others. Precise comparison of different series is not possible without more detailed descriptions of the types of patients and knowledge of the surgical and radiotherapeutic organisation and practice. For the present a reasonable assumption is that, if any difference in survival exists between patients discovered by unselective and selective radiography, it is no more than threefold at five years, and it may be much less. If, therefore, a mass-radiography unit X-rays men over 45 years unselectively it will discover ten times fewer patients with lung cancer than will a unit examining the same number selectively for general practitioners; but about three times as many will survive for five years.

If mass-radiography units could be employed more extensively for unselective radiography, additional cases of lung cancer would be detected before symptoms led the patient to seek the doctor's advice. But it cannot be assumed that all, or even the majority, of cancers can be detected radiographically when the patient has no symptoms, and that intensive, repeated "surveys" will materially decrease the mortality from the disease. Possibly the patient's fate depends more on the inherent malignancy of the neoplasm and its position in the lung than on the efficacy of diagnostic efforts, and his length of life may be largely determined even before the abnormality is detected. To establish the value of repeated radiography, and hence to plan the most effective employment of radiographic resources, requires large-scale, well-planned, purposeful investigations.[7 8] Now that the need for uselective radiography to detect tuberculosis is waning, there is good reason to undertake such studies.

Annotations

EXPERIMENTAL SURGERY AT HAMMERSMITH

MEDICAL research is in the news; but warily we have to find our way between two opposite misconceptions. The ingredients of the first are familiar from pre-war films: the derelict shed at the bottom of the garden, the wonderfully bushy beard bending tremulously over the microscope, yesterday's soup getting cold on the floor amid testtubes and coffee cups and unpaid bills and epoch-making jottings, the ticking of a clock, the spark of inspiration. The second is the streamlined image of today: the billion pound (perhaps we should say rouble or dollar) glass-and-concrete establishment where—remote geographically and in spirit from human civilisation—ant-like creatures with white uniforms and smokeless pipes are busy producing so many medical miracles a day. The difficulty in separating reality from fiction is that there is an element of truth in both. What we tend to forget is that the most sumptuously equipped laboratory is only as good as the best brain working inside it; and that today even the best brain needs material equipment, the cost of which might have kept a whole university in gentlemanly comfort a hundred years ago.

The new department of experimental surgery at Hammersmith, perched on the top floors of a shimmering nine-floor block, is a research-worker's dream: a string of wonderfully spacious laboratories; experimental operating-theatres (equipped with changing, washing, recording, and sterilising rooms that many a non-experimental hospital might envy); animal-houses; a library; a conference room; and, fittingly from the roof, a gorgeous view stretching from the dome of St. Paul's into rural Berkshire. The whole proclaims the generosity of the Wellcome Trust and the enterprise of the University of London, the Medical Research Council, and no doubt many individual patrons of research; the details reflect the careful planning of dedicated teams of research-workers. They have already given ample proof of their capabilities; and the projects now in hand have the right flavour of realism and scientific imagination. One need not be much of a prophet today to predict that organ transplantation and tissue banks will change the face of surgery as completely as did antisepsis and antibiotics in the past (blood-transfusion gives but a foretaste of what is to come); but to embark on this work a few years ago was a bold venture. It has already yielded impressive results: and the new unit promises a brilliant future not only by providing materal facilities but also by bringing home and together the now scattered teams and thus ensuring the intellectual stimulus of discussion and argument. (Much of the work associated in the public mind with " Hammersmith " has, in fact, been carried out in the past by workers from the Hammersmith Postgraduate School at the Buckston Browne Farm, the Royal College of Surgeons, and the Royal Veterinary College). It is also hoped that the new unit will attract other experimental surgical workers—some part-time, others full-time—who have so far lacked the help and guidance of experienced research scientists and technicians, even more perhaps than bench-space. Many a neophyte will no doubt go away with nothing more than a heightened respect for the immense difficulties faced by modern experimental research-workers and a sharpened sense of criticism for unproved claims and fanciful theories; but both these will serve him well.

Prof. Ian Aird, who has been planning and working for this unit ever since he came to Hammersmith thirteen years ago, must be warmly congratulated (though congratulations must surely pall beside the satisfaction of seeing the unit complete) and we express our admiration and good wishes to his numerous collaborators. They include physiologists, pathologists, physicians, physicists, as well as surgeons; and many a small detail in planning and execution bespeaks the skill and experience of the laboratory technical staff. Even without the existing proof of past achievements the visitor to the department soon feels that this is a workshop, not a mausoleum, not just a dream-come-true but a challenge for the future.

THE FIRST BREATH

THE first breath of a newborn infant marks the climax of a dramatic physiological upheaval, but the precise sequence of events is still far from clear. Jäykkä[1] has elaborated the hypothesis that the initial expansion of the

7. Gifford, J. H., Waddington, J. K. B. *Brit. med. J.* 1957, i, 723.
8. Bignall, J. R. *in* Carcinoma of the Lung (edited by J. R. Bignall); p. 171. Edinburgh, 1958.

1. Jaykkä, S. *Acta paediat., Stockh.* 1957, 46, suppl. 112.

lungs is brought about by erection of its vascular framework. Support for this possible architectural role of the pulmonary capillaries was strengthened by Bonham Carter's persuasive analysis.[2]

Jäykkä's hypothesis was attractive in that it linked some apparently unrelated facts. For instance, the high pulmonary-artery pressure at birth and the great increase in pulmonary blood-flow immediately after birth [3 4] seemed ideally suited for capillary erection. Similarly, the newborn infant's transitional circulation through continued patency of the ductus shortly after birth [5 6] invited a new interpretation. Interest focused on the coiled and convoluted configuration of the capillaries between the unexpanded alveoli [7] and their straightening out with expansion. Argument revived over the proper time to clamp the umbilical cord. High venous pressures were claimed to be beneficial in respiratory distress,[8] and new theories of the hyaline-membrane formation were put forward.[9]

The effect of pulmonary vascular distension has been re-examined by workers at the Harvard School of Public Health.[10] In excised, gas-free lungs of cats, puppies, and stillborn infants they studied the pressure changes produced in the closed trachea by varying known fluid pressures in the pulmonary vascular bed. It was shown that the potential inflating force in the trachea was negligible, and, even with a vascular pressure as high as 80 cm. H_2O the airway pressure never exceeded -5 cm. The presence of amniotic fluid tended to negate this small effect. Any increase of the vascular pressure beyond 80 cm. H_2O produced pulmonary oedema. When this occurred, the airway pressure not only returned to atmospheric level but often became positive.

It has long been known that pressures of the order of 35 cm. H_2O are required to inflate the excised newborn lung.[11] Translation of such data to the state in life is difficult owing to the unknown chest-wall compliance; and intra-oesophageal pressure swings of 90 cm. H_2O have been recorded during the first breath.[12] Thus the small airway pressures created by vascular distension can be regarded as an insignificant contribution to the forces needed in the expansion of the newborn lung. The Harvard workers have advanced an interesting alternative explanation for Jäykkä's findings—namely, that the high pulmonary-artery pressure (80 mm. Hg) distended the alveoli with oedema fluid which, when washed away in fixing, gave the illusion of alveoli inflated by gas, and this would also account for changes in total lung volume.

Thus the pendulum of opinion must again revert to established concepts. The high pulmonary-artery pressure at birth is but a temporary heritage of the foetal state, when it is related to the high resistance of an intensely coiled capillary network. This arrangement, in turn, is destined to remain as long as the lungs are unexpanded, and the pulmonary blood-flow is effectively restrained until the onset of respiration. The birth process brings numerous external and chemical stimuli, the respiratory centre responds, and the infant takes the first breath. As the alveoli open, so the capillaries unfold, their resistance falls, and blood rushes into the lungs. Soon the left atrial pressure rises and the foramen ovale closes. The increasing arterial oxygen saturation stimulates the ductus to constrict [13] but the systemic-pulmonary gradient cannot be overcome at once, and blood flows temporarily from aorta to pulmonary artery. This arrangement may aid oxygenation, but there can be no teleological solace in the fact that profound anoxia may reverse the entire sequence.[14]

JOURNEY INTO SPACE

THE return of the two monkeys, Able and Baker, from a high-speed rocket flight to a height of 300 miles [15] emphasises the nearness of manned space travel. We now know that the acceleration and deceleration velocities required to lift a capsule outside the earth's atmosphere and to return it to earth can be borne by primates. The programme of Project Mercury aims for manned space flight in 1961; and already seven American Service aviators have been chosen.[16] The plan is for them to man small earth satellites and to make three ninety-minute-orbits around the world; their altitude will be about 125 miles high and their orbiting speed some 18,000 m.p.h.

Space scientists see manned satellites on the fringe of space as a definite objective which will soon be accomplished.[17]

True space flight with lunar or interplanetary exploration is a long-term target. White [18] points out that a one-way trip to the planet Pluto at supersonic speed would occupy fifty years, and a journey to further stars would be reckoned in centuries. Man could tolerate a flight only of hours in a sealed compartment with the equipment and supplies at a level likely to be afforded by present-day rockets and fuels. Further progress depends on the ability of physiologists to provide a closed, re-cycling ecological system within the space vehicle. Such a system might enable man to take advantage of the rocket systems which could reach the moon. A manned lunar probe would involve a flight lasting weeks. A further obstacle to a lunar probe is radiation. The American "Explorer" satellites have disclosed an intense band of radiation enfolding the earth, known as the "Van Allen belt".

As with all pioneering ventures the problems of selection of personnel loom large.[19] Individual tolerance to acceleration and deceleration forces, and to changes in gravity and atmospheric pressure vary. It is reasonable to select only those who are both supremely fit and constitutionally excellent in these regards. Lonely ventures into the unknown, with the handicap of weightlessness and the thought of an uncertain outcome, call for dedication; and high intelligence is a further requirement in view of the complexity of the instruments. Some of the necessary attributes can already be tested by the specialist in aviation medicine; but new tests will have to be devised as further data are accumulated concerning the exigencies of high-speed space flight.

APPOINTMENT VACANCIES

We regret that the index to announcements of vacancies must be omitted so long as *The Lancet* is printed abroad.

2. Bonham Carter, R. E. *Lancet*, 1957, i, 1292.
3. Adran, G. M., Dawes, G. S., Prichard, M. M., Reynolds, S. R. M., Wyatt, D. G. *J. Physiol.* 1952, **118**, 12.
4. Rowe, R. D., James, L. S. *J. Pediat.* 1957, **51**, 1.
5. Dawes, G. S., Mott, J. C., Widdicombe, J. G., Wyatt, D. G. *J. Physiol.* 1953, **121**, 141.
6. Adams, F. H., Lind. J. *Pediatrics*, 1957, **19**, 431.
7. Reynolds, S. R. M. *Amer. J. Anat.* 1956, **98**, 97.
8. Bonham Carter, R. E., Bound, J. P., Smellie, J. M. *Lancet*, 1956, ii, 1320.
9. Jäykkä, S. *Acta paediat., Stockh.* 1958, **47**, 484.
10. Avery, M. E., Frank, N. R., Gribetz, I. *J. clin. Invest.* 1959, **38**, 456.
11. Wilson, J. L., Farber, S. *A.M.A. J. Dis. Child.* 1933, **46**, 590.
12. Donald, I., Kerr, M. M., Macdonald, I. R. *Scot. med. J.* 1953, **3**, 151.
13. Born, G. V. R., Dawes, G. S., Mott, J. C., Rennick, B. R. *J Physiol.* 1956, **132**, 304.
14. James, L. S., Rowe, R. D. *J. Pediat.* 1957, **51**, 5.
15. *Times*, May 29, 1959.
16. *New York Times*, April 10, 1959.
17. *U.S. Armed Forces med. J.* April, 1959.
18. White, M. S. *ibid.* p. 441.
19. Morrison, J. McC. *Med. J. Aust.* 1959, i, 461.

Points of View

SELF-EXAMINATION: A PROPOSAL FOR ITS SYSTEMATIC DEVELOPMENT

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A FILM, sponsored by the American Cancer Society, which recommends periodic self-examination of the breasts for the early detection of cancer in women, raises the question whether self-examination could reasonably be extended not only to other diseases but to the health examination as a whole.

COMPILING THE SCHEDULE

At first sight it would not seem impossible to draw up a schedule for a self-examination. For instance, records of weight, tests of sight and hearing, skin inspection for cancerous and other lesions, exercise-tolerance tests, and even some laboratory tests, more obviously of urine, might all be undertaken by people for themselves. Indeed, a person might be required to take the initiative in arranging for more specific investigations, such as chest radiography.

But a vital part of the clinical examination is the case history, and without a substitute for this a self-examination would lose some of its value.

In the United States questionnaires are used as a preliminary diagnostic procedure. The Cornell medical index, for example, was found to reveal serious disorders which were overlooked in the hospital.[1] A modified version of this kind of questionnaire, with a guide sheet, might enable the adult to recognise obvious changes in his physical and mental health and to interpret his observations at least roughly. But he would have to appreciate what indications should send him to his doctor, and it should be made clear to him that self-examination is a supplement to, but never a substitute for, a medical examination.

By successive periodic self-appraisals, the patient would gradually gather a cumulative record, which would be valuable to his doctor. Appropriate examinations might also be designed for parents to use on their children. Vollmer[2] has already suggested that mothers might use the tuberculin patch test.

PROS AND CONS

At first sight many people will be inclined to reject the whole idea out of hand. Surely, they will say, to encourage the self-examination is also to encourage both self-diagnosis and self-medication. And self-medication violates the cardinal medical injunction to the layman not to doctor himself.

More dispassionate second thoughts may suggest other considerations. The layman, or the patient if you like, is now, and always has been, the first diagnostician. He decides whether he is well or ill, what home remedies to use, what is good or bad for him, and whether he needs to consult his doctor. Rightly or wrongly, he has theories about medicine and ideas about his own and his family's health. Already he is not only a "self-examiner" and "self-diagnostician", but a "self-therapist", and he usually goes to the doctor only when his own system of self-care breaks down.

Moreover, he has easy access to many sources of information, ranging from friends and relatives to "home doctor" publications. Through the press, radio, and television, advice about symptoms to watch for, remedies to take, and preventive measures to observe are pressed on him by sponsors of commercial products and by unqualified "health experts". It is also, of course, given him increasingly by professional people and professional agencies. Organisations with interests in diseases, such as cancer, tuberculosis, and heart-disease, warn people to watch for symptoms; and many reliable and informative books are written by doctors for laymen.

Against this background of uncontrolled medical advice, the controlled self-examination, which the layman might be trained to do by his own family doctor, could be defended on the grounds that it is a joint venture drawing doctor and patient together, and an effective auxiliary procedure to medical care.

In old age, disease tends to assume a deceptive benignity that veils its insidious development, and with an ageing population we are faced with the need to familiarise the public with premonitory symptoms of disease—but without producing a neurotic preoccupation with ill health. This educational task may well be crucial for the future of public health and medical care, and a controlled examination that enables the adult to appraise his own health regularly may well be part of the answer.

Admittedly, it may be argued that if doctors encourage self-examination, they may also encourage hypochondriasis. But the adult who compulsively carries out elaborate rituals about his health, or who has a disease phobia, has already a serious neurotic disturbance which education or advice will scarcely affect one way or another. To persuade stable people to carry out self-examination flexibly and intelligently will not make them neurotic. Indeed, far from increasing their anxiety, it may increase their feeling of security. Even for the frank hypochondriac self-examination, however compulsively performed, would be preferable to the many ill-informed procedures at present in vogue.

THE DOCTOR'S REACTION

The doctor may well be reluctant to accept a technique that seems to threaten his professional position. And self-examination certainly would be a threat if it "ran away" from medical control and became simply a subject of public propaganda, for which kits and sets of instructions were sold on the open market.

But this is really a misconception. Self-examination should be a private matter arranged between doctor and patient, though it might be supported by reputable public education programmes.

In principle, self-examination is less novel than appears at first sight. The family doctor has always advised his patients to watch for certain symptoms, to take certain steps himself and to return for professional examination in certain circumstances. Self-examination only extends this principle into general and more regular examinations in the normal intervals between the visits of the apparently healthy to the doctor.

As a campaign for sef-examination for breast cancer has already been started this procedure is worth closer inspection as a neat, if involuntary, pilot experiment.

It is a procedure encouraged by reputable public education programmes. The woman is privately taught by her own doctor how to make the examination. She is not expected to make a diagnosis. She is trained to detect breast masses which may or may not be malignant. This issue is not for her, but for her doctor, to decide. The examination is therefore not a substitute for medical diagnosis but a supplement to it. It improves the patient's skill as a first diagnostician and makes possible earlier medical care.

1. Erdman, A. J., Jr., Brodman, K., Lorge, I., Wolff, H. G. *J. Amer. med. Ass.* 1952, **149**, 550.
2. Vollmer, H. *A.M.A.J. Dis. Child.* 1957, **93**, 396.

If we think of a general self-examination along these lines, we recognise it as a cooperative venture between physician and patient, which may help to achieve earlier and more comprehensive diagnosis.

IN STEP WITH THE TIMES

Today great value is attached to the individual, his self-reliance, his sense of responsibility, his freedom to make decisions, and his education. We are therefore inclined to suspect any philosophy which would withhold knowledge from the people. This modern attitude has led to the steady growth of health education. We try to help the individual to be more intelligently aware of matters affecting his health, and to gain his active co-operation in maintaining it. Teaching the patient, not only the technique of self-examination, but also something of its meaning and interpretation, its significance and its limitations, could readily fall into place as part of this movement.

But self-examination cannot succeed without the help of the doctors. We must look to them to draft in detail the items to be included in the examination, to devise simple and practical methods for the patient to apply, and to train him in their intelligent use.

Dr. E. M. Cohart, formerly of the Yale Department of Public Health, is not responsible for any of these views; but I wish to express my appreciation for conversations with him before I wrote this article.

In England Now

A Running Commentary by Peripatetic Correspondents

I've awful bad nightmares,
Which keep coming back,
When my two thousand units
All give me the sack.

Sometimes the dream's different,
It still isn't right.
My two thousand patients
Keep sending all night.

They ring at the front door,
They call on the phone,
They bang at the windows,
They shriek and they groan.

The dream goes on changing;
Each time it gets worse:
My car breaks down hourly,
I borrow a hearse.

The patient are upset,
They write to complain,
They collapse in hysterics,
On me put the blame.

I'll stop eating cheese
The last thing at night;
I'll drink up my hot milk
And put dreams to flight.

My night calls have dwindled,
My car runs like new.
I've no time for nightmares,
I've too much to do.

* * *

It seems that television has now become completely incorporated into our daily lives. While examining a patient the other day, I had occasion to ask if her vision was normal. She replied: "I'm afraid I haven't got one".

* * *

There was a young lady called Topsy
Who was rather too thin for a popsy.
So to fill out her curves
She ate salted preserves,
But the only result was a dropsy.

Letters to the Editor

BREAST CANCER

SIR,—Professor Platt's suggestion (June 20) that the better results of cancer treatment may have nothing to do with "the earlier reference of the patient for treatment" might be compared to spotting a traveller on a 7-mile walk. If he is spotted at the first mile he will then have 6 more miles to go. But if we wish to attack the fellow it is not the milestone that he has reached which is important, but his fighting condition.

Surely Professor Platt has not fallen into the error of confusing "early diagnosis" with "early stage diagnosis". Although the staging of cancer by different individuals is unsatisfactory, there is no doubt that early-stage cases are more "curable" than late-stage cases. The stage at any particular time (or milestone) depends upon the nature of the individual tumour, which unfortunately cannot be judged even by histology, and even in the fourth year the tumour may still be in an "early stage". If, however, cancer is believed to be a progressive disease, it must have been at some time in an "early stage", and therefore Rosahn is probably correct in stating that the better five-year results in recent years are due to the earlier reference of patients for treatment.

Cancer Information Association, Oxford. MALCOLM DONALDSON.

BOXING

SIR,—Those who like boxing—or at least amateur boxing—justify this by claiming that it is "character forming" and that it teaches all sorts of virtues including, particularly, "courage" and "self-reliance". Have they any evidence for these beliefs? Even if they could show that boxers as a group excelled in these qualities, it could be equally argued that this was because boys with these characteristics took up boxing. I have not myself found that boxers always have these virtues. In a good many years' experience of schools, universities, and boys' clubs I have come across many boxers who are admirable citizens, and some who are delinquents and spivs. No figures exist showing the proportion of "good" and "bad" citizens in the whole population and among that section which boxes, but I should be surprised to find a great difference. There is, however, no doubt that learning to box does not *necessarily* make a bad type into a good one!

I suspect that claims that boxing (or even cricket) transforms the character are just a typical piece of British hypocrisy. Those who enjoy these activities should be honest and acknowledge that their motive is enjoyment and nothing else.

London, S.W.I. KENNETH MELLANBY.

EMERGENCIES AT SEA

SIR,—It was a pity that Dr. Hall marred an otherwise admirable article (June 20) by a ten-line paragraph headed Mental Illness, in which diagnoses were replaced by three clinically meaningless labels, one a mere generalisation, the other two terms of abuse; while reference to treatment was virtually confined to the need for circumspection on the doctor's part to ensure personal safety when asked to approach a disturbed or frightened patient. The presumably misplaced faith of laymen in a doctor's capacity to deal kindly and competently with such emergencies, received condescending mention as an additional professional hazard.

This was the only paragraph in the article characterised by a combination of implied distaste and ostensibly invincible indifference to the first principles of the subject. It would have been easy, and brief, to say that throughout the whole range of mental illness encountered as an emergency at sea, from excessive fear or unhappiness, right through to panic or desperation, a consistent attitude of calmness and kindness, tempered by imagination and untroubled by fear, would be not simply the most humane but also the most clinically effective equipment. This statement would also have been true.

As it was, that paragraph, lacking in precept and lamentable in example, seemed to at least one reader unworthy equally of author and subject.

Guy's Hospital, London, S.E.1. D. STAFFORD-CLARK.

Public Health

FAMILY HELPS

Mothers' helps and home helps are already recognised as valued props to mothers and homes. The experimental scheme which the Middlesex County Council is starting in one of their areas lives up to its name and offers help to the family as a whole. Its chief purpose is to allow a family that has got into difficulties, perhaps through illness, perhaps through fecklessness, to survive the emergency without leaving their home. Where necessary family helps will take the place of the mother, and keep the housework going and the children together in familiar surroundings until the mother returns or recovers. According to circumstances, the family help will come and live with the family and take full responsibility, or she will look after the family only during the day and a father or other relative will take over at night. Where the mother remains at home, but is felt to be in need of some training, the family help, under the direction of a health visitor or home organiser, will advise her on budgeting and household management. There will be an agreed scale of charges for the service, but these will be adjusted according to the family income.

STATISTICS FOR FIRST QUARTER

In his latest quarterly return[1] the Registrar General gives some provisional figures for England and Wales in the first quarter of this year. The live-birth rate was 17.2 per 1000, the same as in the corresponding quarter in 1958, compared with an average rate of 16.0 for the years 1953—57. The births registered exceeded the deaths by 14,798; the corresponding figures for the quarters of 1958, 1957, and 1956 were 27,172, 49,307, and 8859 respectively.

The infant-mortality rate for the quarter was 24.7, the lowest ever recorded in this country for a March quarter. On the other hand deaths totalled 176,901, giving a rate of 15.9 per 1000 population — the highest since the March quarter of 1951, when the rate was 19.1. Deaths from influenza (of which there was an epidemic in this March quarter) were 624, compared with 170 in 1958 and 32 in 1957.

Accidental deaths in the March quarter totalled 4623, an increase of 38 for the March quarter of 1958. Deaths due to accidents in the home numbered 2381, and due to coal-gas poisoning 358, compared with 2206 and 263 in 1958 respectively.

Provisional figures for 1958 show that death from coronary heart-disease again increased to 84,048 (76,324) giving an annual death-rate of 1.86 per 1000 population (1.70) (figures for 1957 in parentheses). Deaths from bronchitis numbered 29,392 (26,935). Deaths from cancer of the lung and bronchus were 19,809 (19,119).

In 1958 there was a record low number of deaths from scarlet fever and also from whooping-cough at 4 (10) and 27 (88) respectively. There was 1 death from smallpox and 8 from diphtheria, of which 4 occurred in the Greater London area. Deaths from accidents involving motor vehicles numbered 5438 (4898).

1. Registrar General's Quarterly Return for England and Wales: Quarter ended March 31, 1959. H. M. Stationery Office. Pp 28, 2s

Obituary

HARRY OSBORNE

M.D. Vict., D.P.H.

Dr. Osborne, who was medical officer of health for Salford from 1922 to 1941, died on June 21 at the age of 83.

He qualified from the Manchester Medical School in 1898, and after some years in general practice in Yorkshire he took the D.P.H. in 1907. The following year he joined Salford's school medical service as assistant school medical officer. Ten years later he became deputy M.O.H., and in 1922 he was appointed M.O.H.

A colleague writes:

"In the days when public opinion was far from convinced of the need to protect children from diphtheria, Dr. Osborne organised a campaign against the disease. He also persistently advocated, against opposition as well as apathy, the increasing use of smokeless fuels. Outside his work his consuming interest was the study of the penny black and twopenny blue stamps. He brought an expert eye and new techniques to the detection and classification of flaws in the plates and printing, and in the philatelic world his beautifully illustrated books are accepted as the foremost contribution on the subject."

Dr. Osborne was a widower. Two of his three sons became doctors. One died of poliomyelitis while serving with the Forces as a medical officer in Egypt. The other is a plastic surgeon on the staff of the Royal Liverpool United Hospitals.

Dr. GRANTLY DICK-READ

An American correspondent writes:

"Dick-Read will be remembered as a man who made a lifetime pursuit of an idea which is becoming fundamental in modern obstetrics—namely, that with preliminary training and skilful attendance most women can go through childbirth with a minimum of discomfort and with a heightened sense of satisfaction. To reduce fear he advocated instructing the mother in the physiology of birth and to reduce muscular tension he recommended the 'progressive relaxation' techniques of Edmund Jacobson of Chicago. In 1947, he lectured in the United States and as a result of this visit and one by a coworker, Mrs. Helen Heardman, the department of obstetrics and gynecology at the Yale School of Medicine, with the support of the Maternity Center Association of New York, embarked upon a study of Dick-Read's methods and their application to hospital practice—the first approach to the subject in a teaching hospital. The result is seen in the preparation-for-childbirth programme at the Yale Medical Center in New Haven, now in its 13th year. While the Yale programme does not follow many of Dick-Read's recommendations it has proven to most observers that for many women intelligent preparation for childbirth yields gratifying results.

"Read never insisted upon complete omission of anæsthetics or analgesics in childbirth. In his own words, 'Pain is the only justification; it does not matter whether the pain is secondary to fear or whether it is primarily physical.' In his own country Dick-Read became a controversial figure chiefly because of his disbelief in the existing order of obstetrical procedure and his outspoken expression against those who did not share his views. In letters to friends in America he always expressed deep disappointment over the slow recognition accorded to what he considered was obstetrical progress. However, in later years he had satisfaction in seeing that much of his basic thinking about the psychology of childbirth was gaining wide acceptance. From present evidence in American obstetric texts and clinics, it is likely that his name will be regarded as one of historic significance for many years to come."

Births, Marriages, and Deaths

DEATHS

McDADE.—On June 4, Robert Sinclair Charles McDade, aged 54, at Roselands, Broomfield, physician, Broomfield Hospital, Essex.

Notes and News

QUEEN ELIZABETH COLLEGE

Situated in Campden Hill Road, W.8, the Queen Elizabeth College of London University is the only institution in this country that provides courses leading to a degree in nutrition (B.Sc. Nutrition, London). The new laboratories, of which Sir John Atkins laid the foundation stone on June 24, will permit much-needed development. Research in the college, and particularly in its nutrition department, has been hampered by lack of accommodation; but in the new buildings, which will house the departments of bacteriology, biology, and nutrition, far more should be possible. These buildings have been named after Sir John Atkins, who has been associated with the college for nearly fifty years.

A FILM ON GENERAL PRACTICE

A lively and entertaining film on general practice had its first showing on June 18 in London, at the Royal College of Surgeons, before a large audience, which included the Minister of Health. The film, which was made for the *Medical World*, was directed by Paul Dickson, and sponsored by Messrs. Lloyd-Hamol. Its aim (and that of the series of which it is the first) is to stimulate thought and discussion about the role of the general practitioner in Britain today, and this it effectively does by brisk presentation and skilful commentary on the work of the general practitioner and its relationship to other parts of the National Health Service. Sir Russell Brain contributes a wise postcript to the film, which will, we hope, be widely seen and discussed.

Its next showing will be at the B.M.A. scientific conference in Edinburgh later this month and it can be seen again in London at the *Medical World* conference on Oct. 18. Thereafter the film will be available for showing to audiences of doctors, medical students, and social workers.

The film (16 mm., black and white, sound, 30 min.) is entitled *Enquiry into General Practice* and will be obtainable through the B.M.A. Film Library and Sound Services Ltd., free of charge to approved audiences. Until final arrangements have been made for distribution, preliminary inquiries for booking should be addressed to *Medical World*, 56, Russell Square, London, W.C.1.

University of London

Dr. J. L. D'Silva, professor of physiology at London Hospital Medical College, has been appointed to the Halliburton chair of physiology at King's College, and Dr. Derrick Dexter, senior lecturer at St. George's Hospital Medical School, to the readership in morbid anatomy at that school. The title of reader in therapeutics has been conferred on Dr. J. R. Trounce in respect of his post at Guy's Hospital Medical School.

University of Liverpool

Dr. T. Cecil Gray, reader in anæsthesia, has been appointed professor of anæsthesia.

Dr. Gray, who is 46 years of age, was educated at Ampleforth College, York, and the University of Liverpool, where he qualified in 1937. After spending six years in general practice he was appointed demonstrator in anæsthesia in the University of Liverpool and in 1947 he was appointed reader. He also held appointments as anæsthetist in the Royal Liverpool United Hospitals and the Liverpool Chest Surgical Centre. He became a senior honorary anæsthetist to the Royal Liverpool United Hospitals in 1946, and he was elected F.F.A.R.C.S. in 1948.

Dr. E. Sherwood Jones, lecturer in the department of medicine, has been appointed senior lecturer.

University of Bristol

At recent examinations for the degrees of M.B., Ch.B. the following were successful:

Patricia C. Clegg, P. R. Golding, Sara J. Harries, M. S. Knapp, Sylvia J. Smith (second-class honours); Anne F. M. Bracey, R. M. Carr, A. J. Cooper, John Cooper, Mollie Dada, J. W. Davies, S. T. de Garis, Ebong Samson Etuk, R. B. Goffin, J. A. A. Hakes, Valerie J. Howard, C. F. Lipscomb, Patricia M. Lovell, J. Adegboyega Olajide Magbagbeola, R. V. Magnus, T. A. Medway, A. G. Nash, Oyinade Odusola Odutola, Cambyse Panahy, D. W. Pilton, Patricia Stant, Hans Steiner, D. W. Sykes, M. O. Symes, M. A. Voyce, D. H. Wale, Anna G. Walker, I. R. Walker, A. G. White, A. M. Wilson.

University of Birmingham

Dr. L. T. Clarke and Dr. B. L. S. Murtagh have been appointed lecturers in anæsthetics and Dr. A. J. Essex-Cater lecturer in child welfare in the department of pædiatrics and child health.

University of St. Andrews

Dr. Alwyn Smith has been appointed lecturer in public health and social medicine at Queen's College, Dundee.

Royal College of Surgeons of England

At a meeting of the council on June 11, with Sir James Paterson Ross, the president, in the chair, the Lady Cade medal was presented to Squadron-Leader T. C. D. Whiteside, and the Hallett prize to Dr. D. F. Weinman (Ceylon).

The following were coopted to the council for the year 1959—60, representing various branches of practice:

Dr. J. H. Hunt, general practice; Dr. G. S. W. Organe, anæsthetics; Mr. T. Keith Lyle, ophthalmology; Mr. A. C. H. Bell, gynæcology and obstetrics; Prof. D. W. Smithers, radiology; Mr. C. Gill-Carey, otolaryngology; Sir Wilfred Fish, dental surgery.

A diploma of membership was granted to E. M. Blenkinsopp.

Royal College of Surgeons of Edinburgh

On Friday, July 10, at 3.30 p.m. at the college, Nicolson Street, Edinburgh, 8, Prof. W. C. MacKenzie will give a lecture on islet cell tumours and peptic ulcers.

Royal Australasian College of Physicians

At a meeting of the general body of fellows of the college held in Adelaide on May 27 the following were elected and admitted to fellowship:

Under article 44: J. C. Belisario (New South Wales); Muriel E. Bell (New Zealand). *Under article 42:* D. A. Ballantyne, J. V. Cable, O. W. Chapman, J. A. K. Cuningham, A. O. M. Gilmour, D. McR. Hanna, J. R. Hinds, K. H. Holdgate, J. A. Kilpatrick, E. G. McQueen, J. L. Newman (New Zealand); M. W. Fletcher (Tasmania); Leo Flynn, R. L. Harris, P. J. Markell, Willa Nelson (New South Wales); H. R. Gilmore (South Australia); Bryan Hudson, W. Hamilton Smith (Victoria); W. B. Macdonald, W. R. Pitney (Western Australia).

The following were admitted to membership:

J. C. Biggs, T. Burfitt-Williams, A. H. B. Chancellor, E. G. Cleary, W. R. Hobart, J. E. Jefferis, David Jeremy, G. J. Morgan, J. J. Morgan, M. R. Playoust, James Rankin, F. X. M. Willis (New South Wales); W. C. Boake, H. D. Breidahl, J. A. Brenan, K. D. Muirden, J. R. Syme, D. C. Wallace, J. S. Yeatman (Victoria); P. S. Hetzel, G. A. Hunter, J. L. Waddy (South Australia); J. J. Eadie (Queensland); M. N. I. Walters (Western Australia). *Under article 37:* E. S. Finckh (New South Wales); R. T. W. Reid (South Australia).

Society of Apothecaries of London

The diploma of M.M.S.A. Lond. has been awarded to D.L. Sladden, and the following have been granted the L.M.S.S.A.:

J. J. O'Donnell, C. Dunster, A. M. Sherrington, G. R. Graham, B. H. Hamilton, M. G. Royle, T. A. Thorburn, J. C. Roberts, M. J. Streule, S. H. N. Pratt, B. Malek, R. G. Holmes, P. J. A. V. Willems, H. Bayoumi, A. S. Horniblow, M. H. Marsh, P. Williams, R. E. Kendell, I. K. Dajani, J. A. Bushman, S. L. Geoghegan, R. K. Elias.

Institute of Dermatology

On Tuesday, July 14, at 5.30 p.m., at the institute, Lisle Street, London, W.C.2, Dr. T. H. Sternberg will give a lecture on griseofulvin.

An Industrial Court award has laid down new salary scales for radiographers. The present basic salary scale is to be raised from £420—£485 to £500—£600 and that for superintendent radiographers from £675—£810 to £810—£980. The award is retrospective to Feb. 1, 1959.

The Society for the Study of Addiction will hold its annual general meeting on July 14, at 8 p.m., at 11, Chandos Street, London, W.1.

CORRIGENDA:

Bisacodyl: an Evacuant Drug.—In this article (June 6 p. 1173) the opening sentence of the penultimate paragraph read "bowel emptying was good or adequate in 80". In fact this figure should have been 88.

Trauma and Squamous Skin Cancer.—In Dr. Gillett's letter of June 13 the number of cases in which lesions had been sent to him for histological examination should have been 32 and not 12.

Breast Cancer.—In the 6th line of the second paragraph of last week's letter by Dr. Ellison Nash (p 1283) "operative" should have read "operable".